US Army Medical Command, Falls Church, Virginia

CLINICAL GUIDELINES FOR MANAGING ADVERSE EVENTS AFTER VACCINATION

April 2003 Edition

1. Purpose: To help medical personnel individually manage and document adverse events after vaccination. Based on clinical experience with adverse-drug-reaction management and with vaccine delivery in general, this document offers treatment and reporting recommendations. Adapt these guidelines to individual clinical cases, according to the judgment and scope-of-practice of the health-care provider.

2. Adverse Events After Vaccination: Most people tolerate vaccination without significant side effects. But adverse events may occur after vaccination, sometimes requiring treatment to relieve symptoms. Although many side effects respond to self-medication, people experiencing an adverse event should advise a health-care provider before the next dose of the same vaccine. Several studies indicate that women are more likely than men to experience temporary injection-site reactions and systemic symptoms that typically resolve on their own.

a. *Injection-site reactions, such as redness and swelling.* These reactions are not unusual. Antibiotics are not typically warranted to treat injection-site reactions. Anthrax vaccine, administered subcutaneously (SC), is associated with a high frequency of nodules (also called knots or lumps). Although mild to moderate local reactions can be self-medicated, worsening local reactions should be reported to a health-care provider and documented in the medical record, before the next dose.

b. *Systemic events, such as immediate hypersensitivity, fever, or muscle aches.* Systemic events are less common than injection-site reactions, and may or may not be caused by the vaccine. Systemic events may appear later after vaccination than injection-site reactions.

c. *Vaccination and the differential diagnosis.* Some events are caused by vaccination. Others simply coincide in time and may be unrelated to the vaccine. The frequency of the events listed in the attached tables is not uniform. Some are common, while others are rare, if they occur at all. Events may occur that are not listed. Regardless, it is paramount for health-care providers to provide the best care possible for the person in need, regardless of causality. Identify and document clinical problems that follow vaccination before the next dose. Vaccination should be considered in the differential diagnosis, as clinically appropriate. When planning future actions, assess the risk-benefit ratio for continued vaccination versus medical exemption.

d. *Additional evaluations.* While most adverse events after vaccination require no treatment, some people may need further evaluation, therapy, and/or exemption from further doses of the vaccine. Document all adverse events requiring pre-vaccination treatment, post-vaccination treatment, relief from work, hospitalization, or other medical care on the Service's clinical-encounter form. Report as discussed below.

3. Treatment Guidelines: See algorithms depicted in Figures 1, 2, and 3, plus companion tables with text-based details. Based on published literature and clinical experience, these guidelines are divided into two major groups: injection-site reactions and systemic events. Consider relevant footnotes. Patients may present with symptoms corresponding to more than one category.

4. VAERS Reporting:

a. Adverse events after vaccination are reported to the Vaccine Adverse Event Reporting System (VAERS) using the official VAERS form. DoD and the Coast Guard require submission of a VAERS report, *at a minimum*, for adverse events after vaccination that involve hospitalization, a life-threatening event (such as anaphylaxis), loss of duty of 24 hours or longer, or an event related to suspected contamination of a vaccine vial. These are minimum requirements. The Department encourages clinicians to report all other clinically relevant adverse events after administration of any vaccine or medication to VAERS or MedWatch.

b. Clinicians who file a VAERS report are not making a determination that the two events are linked in a cause-and-effect manner. Ideally, initial VAERS forms should be submitted by primary-care providers, with follow-up VAERS forms filed by subspecialists as additional information comes to light. Anyone identifying a qualifying case, and uncertain whether a VAERS report was submitted previously, should submit one.

c. If the patient considers his or her adverse event significant and due to the vaccine, the clinician should file a VAERS report. Vaccine recipients may complete VAERS forms themselves and submit them directly to the Food & Drug Administration (FDA). Reporting by a health-care provider is preferred, to enhance the quality and completeness of the clinical data reported.

d. VAERS forms may be downloaded from the Service surveillance centers, or from www.anthrax.mil/vaers/vaers.htm. Additionally, one may obtain VAERS forms by contacting VAERS at 1-800-822-7967 or www.vaers.org.

e. Attach pertinent information from the vaccine recipient's medical record to the VAERS report. Forward the original VAERS form and attachments `to VAERS, P.O. Box 1100, Rockville, MD 20849-1100. At the same time, send a copy of the VAERS report and attachments through the local Preventive Medicine or Preventive Health Officer, as applicable, to the Service surveillance center (Annex A). Reports also should be submitted to the local pharmacy-and-therapeutics (P&T) committee, because institutions have an accreditation requirement to encourage adverse-drug-reaction reporting. Do not delay reporting while awaiting a P&T committee meeting. Pharmacists can assist in filing VAERS reports.

f. The Department of Defense forwards all VAERS reports to the FDA and the Centers for Disease Control & Prevention (CDC) without restriction. VAERS reports on anthrax vaccine are reviewed for causality by the FDA and CDC, as well as an independent civilian committee, known as the Anthrax Vaccine Expert Committee (AVEC), under the auspices of the U.S. Department of Health and Human Services.

5. Medical and Administrative Exemptions:

a. Good medical practices for the management of an adverse drug reaction apply to the evaluation of any adverse event after vaccination. Good medical practices also apply to the medical-decision process for granting exemptions or continuing to vaccinate in the face of an adverse event potentially linked to vaccine administration.

b. The primary-care provider may grant indefinite medical exemptions. However, if additional clinical consultation is needed to assess a patient's condition, the primary-care provider should perform the initial clinical work-up appropriate to the presenting symptoms. Under these conditions, primary-care providers may grant a temporary medical exemption pending the results of a referral to a subspecialist appropriate to the individual's clinical condition (e.g., dermatology, neurology,

otolaryngology, rheumatology, allergy/immunology). Multidisciplinary consultations may be appropriate in some circumstances.

c. Subspecialists may grant indefinite medical exemptions. Return to primary-care providers is not required, if the referring subspecialist deems an indefinite medical exemption is warranted.

d. Granting administrative exemptions is a non-medical function, usually controlled by an individual's unit. Granting medical exemptions is a medical function performed by a credentialed health-care provider. Medical exemptions should be applied only when medically warranted. If the case is complex or not readily definable, a clinical summary should be sent to the regional clinical subject matter expert or group for review. Medical records of Service Members who disagree with a given provider or consultant's recommendations regarding the exemption should be referred for a second opinion to a provider or consultant group with experience in vaccine adverse reaction management. Review exemptions periodically to confirm continued applicability. Use the following exemption codes for electronic tracking of vaccinations.

e. Medical Exemption Codes:

Code	Meaning	Explanation or Example	Duration
MI	Medical, Immune	Evidence of immunity (e.g., serologic antibody test, "take" after smallpox vaccination); documented previous infection (e.g., chickenpox in lieu of varicella vaccine)	Indefinite
MR	Medical, Reactive	Severe adverse reaction after immunization (e.g., anaphylaxis). Code can be reversed if an alternate form of prophylaxis is available. Probably warrants VAERS report	Indefinite
MT	Medical, Temporary	Pregnancy, hospitalization, temporary immune suppression, convalescent leave, any temporary contraindication to immunization	Specified period
MP	Medical, Permanent	HIV infection, pre-existing allergy, permanent immune suppression. Can be rescinded if the condition changes.	Indefinite
MD	Medical, Declined	Declination of optional vaccines (not applicable to many military vaccinations), religious waivers	Indefinite
MS	Medical, Supply	Exempt due to lack of vaccine supply	Indefinite

7. Acknowledgements & Revisions:

a. This revision, the third edition of these guidelines, is issued by the Anthrax Vaccine Immunization Program (AVIP) Agency, within the Office of The Army Surgeon General, Falls Church, Virginia. The guidelines were developed based on published literature and clinical consensus, beginning at the Biological Warfare Defense Immunizations Conference, 25-27 May 1999. The major authors of this document are LTC Phillip Pittman, COL Renata Engler, LTC Bryan Martin, LTC John Grabenstein, along with clinicians from the medical departments of the U.S. Army, Navy, Marine Corps, Air Force, and Coast Guard.

b. This document will be revised periodically, based on clinical experience and epidemiological data. This document provides general guidelines to adapt to individual clinical cases, according to the judgment and scope-of-practice of each health-care provider.

c. Forward suggestions for improvements to this document to LTC John D. Grabenstein, Anthrax Vaccine Immunization Program Agency, fax 703-681-4692, e-mail john.grabenstein@amedd.army.mil. Medical command channels will disseminate revisions periodically, which will be posted on the AVIP website, www.anthrax.mil.

8. Selected Bibliography on Anthrax & Other Vaccines:

a. Advisory Committee on Immunization Practices. General recommendations on immunization. *MMWR* 2002;51(RR-2):1-35. ftp://ftp.cdc.gov/pub/Publications/mmwr/rr/rr5102.pdf

b. Advisory Committee on Immunization Practices. Update: Vaccine side effects, adverse reactions, contraindications, and precautions. *MMWR* 1996;45(RR-12):1-35, errata 227, ftp://ftp.cdc.gov/pub/Publications/mmwr/rr/rr4512.pdf.

c. Advisory Committee on Immunization Practices. Use of anthrax vaccine in the United States. *MMWR-Morbidity & Mortality Weekly Report* 2000;49(RR-15):1-20. http://www.cdc.gov/mmwr/PDF/rr/rr4915.pdf

d. American College of Physicians. *Guide for Adult Immunization*, 3rd ed. Philadelphia: American College of Physicians, 1994.

e. Atkinson W, Wolfe C, Humiston S, Nelson R, ed. *Epidemiology & Prevention of Vaccine-Preventable Diseases*, 7th ed. Atlanta: Centers for Disease Control & Prevention, 2002, http://www.cdc.gov/nip/publications/pink/.

f. Centers for Disease Control & Prevention. Surveillance for adverse events associated with anthrax vaccination—U.S. Department of Defense, 1998-2000. *Morbidity & Mortality Weekly Report (MMWR)* 2000;49(Apr 28):341-5. [reprinted in *JAMA* 2000;283(May 24/31):2648-9] http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/mm4916a1.htm

g. Food & Drug Administration. Post-marketing surveillance for adverse events after vaccination: the national Vaccine Adverse Event Reporting System (VAERS). *MedWatch* November 1998, http://www.fda.gov/medwatch/articles/vaers/vaersce.pdf.

h. Franz DR, Jahrling PB, Friedlander AM, McClain DJ, Hoover DL, Bryne WR, Pavlin JA, Christopher GW, Eitzen EM Jr. Clinical recognition and management of patients exposed to biological warfare agents. *JAMA* 1997;278(Aug 6):399-411. http://jama.ama-assn.org/issues/v278n5/ffull/jsc71014.html

i. Friedlander AM, Pittman PR, Parker GW. Anthrax vaccine: Evidence for safety and efficacy against inhalational anthrax. *Journal of the American Medical Association* 1999;282:2104-6. http://jama.ama-assn.org/issues/v282n22/pdf/jct90025.pdf

j. Grabenstein JD. *ImmunoFacts: Vaccines & Immunologic Drugs*. St. Louis: Facts & Comparisons, August 2002.

k. Inglesby TV, O'Toole T, Henderson DA, Bartlett JG, et al. Anthrax as a biological weapon, 2002: Updated recommendations for management. *JAMA* 2002;287:2236-52, http:// jama.ama-assn.org/issues/v287n17/fpdf/jst20007.pdf.

l. Pittman PR, Kim-Ahn G, Pifat DY, Coonan K, Gibbs P, Little S, Pace-Templeton JG, Myers R, Parker GW, Friedlander AM. Anthrax vaccine: Safety and immunogenicity of a dose-reduction, route comparison study in humans. *Vaccine* 2002;20:1412-20.

m. Pittman PR, Mangiafico JA, Rossi CA, Cannon TL, Gibbs PH, Parker GW, Friedlander AM. Anthrax vaccine: Increasing intervals between the first two doses enhances antibody response in humans. *Vaccine* 2000;18:213-216.

n. Plotkin SA, Orenstein WA, ed. *Vaccines*, 3rd ed. Philadelphia: W.B. Saunders, 1999.

o. White CS III, Adler WH, McGann VG. Repeated immunization: Possible adverse effects: Reevaluation of human subjects at 25 years. *Annals of Internal Medicine* 1974;81:594-600. http://www.anthrax.mil/Site_Files/articles/INDEXclinical/anthraxlibrary/Repeated.pdf.

p. Zimmerman B, Zimmerman RS. Adverse reactions to vaccines. In: Middleton E Jr, Ellis EF, Yunginger JW, Reed CE, Adkinson NF Jr, Busse WW, eds. *Allergy Principles and Practice*, 5th ed. St. Louis: Mosby, 1998:1199-1211.

q. Anthrax vaccine adsorbed, BioThrax, product labeling. Lansing, Michigan: BioPort Corporation, 31 Jan 2002. http://www.anthrax.mil/Site_Files/articles/INDEXclinical/package_insert.htm

r. Joellenbeck LM, Zwanziger L, Durch JS, Strom BL, ed. *The Anthrax Vaccine: Is it Safe? Does it Work?* Washington, DC: National Academy of Sciences, March 2002. xxi + 265 pages. http://www.nap.edu/catalog/10310.html.

Annex A. Service Surveillance Centers

Army Medical Surveillance Activity
Bldg T-20, Rm 213 (Attn: MCHB-EDS)
6825 16th Street, N.W.
Washington, DC 20307-5000
Phone: 202-782-0471 (DSN 662)
Fax: 202-782-0612
http://amsa.army.mil/AMSA/amsa_home.htm

Navy Environmental Health Center
2510 Walmer Ave
Norfolk, VA 23513-2617
Phone: 757-462-5500 (DSN 253), after hours 757-621-1967
Fax: 757- 444-9691
http://www-nehc.med.navy.mil/

Air Force Force Health Protection and Surveillance Branch
Institute for Environment, Safety and Occupational Health (ESOH) Risk Analysis
2513 Kennedy Circle
Brooks AFB, TX 78235-5123
Phone: 210-536-5454 (DSN 240)
Fax: 210-536-6841
http://iera.satx.disa.mil/iera/index.html

Coast Guard Headquarters Directorate of Health and Safety
Commandant (G-WKH)
2100 Second Street SW
Washington, DC 20593
Phone: 202-267-1098
Fax: 202-267-4338

IMMUNIZATION SERVICES: SCREENING QUESTIONAIRE

Please answer the questions below by checking the appropriate boxes (Yes, No or don't Know)

Your careful responses will help us determine which vaccines may be safely given in the clinic today. If the question is not clear, please ask a nurse or doctor to help explain it.

Item Number	Question or Education Point Information	Yes	No	Don't know
1.	Are you sick today?			
2.	Do you have a fever today?			
3.	Do you have **allergies**? Eggs – thimerosal – neomycin – gelatin – rubber / latex – medicines – preservatives - other			
4.	Do you have a **history of adverse events** after ANY vaccine? If yes, please ask for adverse-event form from the front desk.			
5.	Do you take a **blood thinner** like Coumadin or do you (does the child/patient) have a **bleeding problem**?			
6.	Do you have a chronic illness such as: chronic heart, lung, liver, kidney, or skin disease, diabetes, sickle-cell anemia, or had your spleen removed, G6PD, frequent infections? Please describe:			
7.	Do you (or any close contact) have **cancer, leukemia, HIV/AIDS, transplant, or any other immune-system problem**? Do you (or close contact) have a **chronic skin disease, rash or eczema, atopic dermatitis**? Please describe:			
8.	Have you taken **cortisone, prednisone, other steroids, anticancer drugs, or x-ray treatments** in the past 3 months?			
9.	Have you received a **transfusion** of blood or plasma, or been given a medicine called **immune (gamma) globulin** in the past year?			
10.	Could you be **pregnant**? When was your last menstrual period?			
11.	Is there a chance that you could become **pregnant in the next month**?			
12.	Have you received any vaccinations in the last 4 weeks?			
13.	If yes, indicate if any of the following: MMR, measles, mumps, rubella, varicalla/chickenpox, yellow fever, smallpox, anthrax, other:			
14.	Have you has a seizure, brain or psychiatric problem?			
15.	Are you here today to receive the **next shot in a series**?			
16.	If so, please indicate which series? Anthrax – hepatitis A – hepatitis B – Japanese encephalitis (JEV) – rabies – other.			
17.	Are you traveling abroad soon?			
18.	If yes, indicate departure date and countries			

Patient Signature: _____ **Date:** _____

FOR CLINIC USE Reviewing Provider_____ Date:_____
Cleared for Immunization: _____
Not Cleared for Immunization: _____
Other: _____

Example 1. Sample Immunization Screening Questionnaire

IMMUNIZATION SERVICES: VACCINATION FOLLOW-UP

Thank you for completing the following questionnaire regarding your experience with a prior vaccination. Please check YES if you have the type of reaction described after receiving any prior vaccine. If the reaction occurred after a vaccine administered as a series indicate which dose by entering the dose number at the column **D#___**

	Information Elements	**Yes**	**No**	**D#__**	**D#__**
1.	**Vaccine: Date Administered:**				
2.	Indicate in which arm shot was received (R= right or L = left)				
3.	Did you receive educational material or a verbal briefing about the vaccine before series specific dose?				
4.	**Local Reaction at the Sire of the Shot**				
	Pain/reaction limiting motion lasting for _____hours				
	Redness less than 5 cm (<2 inches) lasting for _____hours				
	Redness more that 5 cm (>2 inches) lasting for _____ hours				
	Redness more than 12 cm (>4 inches) lasting for _____hours				
	Swelling from the upper arm to below the elbow lasting for _____hours				
	Itching at the site of the shot lasting _____hours				
	Knot or lump at the site lasting for _____hours				
	Any other local (injection site) reaction(s): _____hours				
	Joint swelling or stiffness lasting more 12 hours in the shot arm				
	Numbness and/or tingling and/or burning in arm of shot site				
5.	**Generalized Reaction:** Immediate (within 60 minutes of the shot)				
	Generalized itching and/or hives				
	Shortness of breath, asthma, chest tightness				
	Loss of consciousness, low blood pressure				
	Acute illness:				
	Did you receive emergency or immediate treatment?				
6.	**Generalized Reaction:** Prolonged or delayed in onset. If none, check NO				
	Generally feeling bad for more than a few hours:_____hours				
	Chills or Fever: How high_____				
	Fatigue lasting more than a few hours: _____hours				
	Headaches:				
	Generalized muscle aches lasting _____hours				
	Joint aches lasting_____ _hours				
	Dizziness or light-headedness lasting_____ _hours				
	Nausea and/or poor appetite lasting_____ _hours				
	Abdominal cramping and/or diarrhea lasting_____hours				
	Ringing in ears lasting_____hours				
	Numbness or tingling or sharp pains lasting _____hours				
	Swollen and/older tender lymph glands lasting_____hours				
	Generalized rashes and/or hives persisting _____hours				
7.	**Impact:** None (able to work, exercise, recreate), check NO. If Yes, describe: Missed work: Yes No Days_____ Missed PT: Yes NO Days:_____				
8.	**Compare your reaction to other vaccines you have received.** Scale 1-5 with 5 = Most severe reaction				
	Name:_____ Date:_____ **Age (at time of reaction)_____ Sex:_____**				

On back of sheet, indicate if seen by a physician and degree to which symptoms have resolved. Please return this form to Allergy-Immunology Clinic

Example 2. Sample Questionnaire for Adverse Events After Vaccination

MANAGING ADVERSE EVENTS AFTER VACCINATION

Service Member Receives Vaccine

***If in yellow or red zone, avoid simultaneous administration with other vaccines.**

NO REACTION

LOCAL REACTION
(More common in women than men)

MILD LOCAL REACTION:
Redness < 50 mm diameter, pain, swelling, itching; lump / nodule (LR1, LR2, LR3)

MODERATE LOCAL REACTION:
Redness 50-120mm diameter, pain, swelling, itching; lump / nodule; numbness, tingling; burning (LR4, LR7)*

LARGE LOCAL REACTION, ± COMPLICATIONS:
Redness >120 mm, pain, swelling to or below elbow; local rash (LR5, LR6, LR8)*

NO REACTION

Educate.

Document.

Continue to screen for exclusion criteria (e.g., steroid therapy, pregnancy). Continue series as scheduled.

MILD LOCAL REACTION

Document.

Educate.

Treat symptoms.[1-4]

Continue series as scheduled. Avoid strenuous exercise for 24 to 48 h after next dose to avoid aggravating local reaction.

MODERATE LOCAL REACTION

Document.
Educate.
Treat symptoms.[1-4,6]
Avoid strenuous exercise.

For moderate reaction, continue series. Before next dose, consider issues of pretreatment,[1,2,4] route,[7] or interval.[8]
If reactions to later doses decrease, continue.
If reactions recur, persist, or worsen: Reevaluate, consider temporary exemption, pending consultation.

LARGE LOCAL REACTION, ± COMPLICATIONS

Document.
Educate.
Take photo.
Consider consulting with next level of care.[6]
Treat symptoms.[1-4]
Submit VAERS report.
Avoid strenuous exercise.

Clinical guidelines for managing adverse events after vaccination: *Version April 2003.* This document provides general guidance, to adapt to individual clinical cases. Use with companion tables. Patients may present with symptoms corresponding to more than one category. Revisions to this document will be disseminated via medical command channels and posted on AVIP site, www.anthrax.mil. The probability of events on this chart is not uniform: some are quite common and some are rare. See cover sheet for details.

Submit VAERS reports as warranted. Must be submitted for hospitalization, loss of duty ≥ 24 h, or suspected vial contamination. Other events may also be reported. Presumption of causation is not required to submit VAERS reports. Forms available at www.anthrax.mil/vaers/vaers.htm.

MANAGING ADVERSE EVENTS AFTER VACCINATION

Service Member Receives Vaccine

***If in yellow or red zone, avoid simultaneous administration with other vaccines.**

SYSTEMIC EVENT

Myalgias, arthralgias, arthritis; headaches; syncope or near syncope; anxiety response. (SE1, SE4, SE6, SE16) *

→ **Document. Educate. Consult as needed. Consider pre/post-treatment NSAID.[1-4] Headache: acetaminophen , ibuprofen, *et cetera*.[1-4]**

→ **For mild to moderate event(s), continue. Before next dose, consider issues of pretreatment,[1,2,4] route,[7] or interval.[8] If tolerates next dose, continue series. If event(s) recur or worsen: Reevaluate; consider temporary exemption and VAERS report, pending consultation.**

"Flu"- or Viral-Like Symptom Groups:

Viral-Like	Respiratory	Gastrointestinal
< 96 h: 3 of these: Temp 100.5-102.5°F (adolescent/adult) or 104°F (children), anorexia/nausea, myalgia/arthralgia, malaise/fatigue, light-headedness, headache (SE2a) (but not SE17 or 18)	Cough, coryza or rhinorrhea, congestion, sore throat. (SE17)	Nausa, vomiting; diarrhea, abdominal pain, gas, indigestion. (SE5, SE18)

***Severe / prolonged*:**
≥ 96 h or T > 102.5 or 104°F (SE3) *

→ **Document. Treat symptoms.[1-4] Educate.**

→ **For mild to moderate event(s), continue. If event(s) recur or worsen: Reevaluate; consider temporary exemption and VAERS report, pending consultation.**

Other events: Fatigue > 60 days; Tinnitus; Vertigo; Idiosyncratic events after live vaccines (SE7, SE15, SE19, SE20) *

→ **Treat acute event. Document. Educate.**

→ **Prompt consult.[5,6] Give temporary exemption pending consultation. VAERS report.**

Clinical guidelines for managing adverse events after vaccination: *Version April 2003.* This document provides general guidance, to adapt to individual clinical cases. Use with companion tables. Patients may present with symptoms corresponding to more than one category. Revisions to this document will be disseminated via medical command channels and posted on AVIP site, www.anthrax.mil. The probability of events on this chart is not uniform: some are quite common and some are rare. See cover sheet for details.

Submit VAERS reports as warranted. Must be submitted for hospitalization, loss of duty ≥ 24 h, or suspected vial contamination. Other events may also be reported. Presumption of causation is not required to submit VAERS reports. Forms available at www.vaers.org.

MANAGING ADVERSE EVENTS AFTER VACCINATION

Service Member Receives Vaccine

***If in yellow or red zone, avoid simultaneous administration with other vaccines.**

SYSTEMIC EVENT

Anaphylaxis, systemic allergic reaction; Angioedema or swelling, Serum sickness (SE11, SE12)*	Other skin disorders: Focal or limited; Generalized skin disorder; Diffuse blistering dermatitis and/or mucositis (SE8, SE9, SE10)*	Neurologic disorder: Peripheral neuropathy; Encephalopathy, Guillain-Barré, Focal neurologic disease (SE13, SE14)*	Other systemic disorder presenting or worsening in temporal association with vaccine
Treat acute event. Document. Educate.	Treat. Document. Educate. Take photo(s). Consider biopsy.	Treat. Document. Educate.	Treat. Document. Educate.
Prompt allergy consultation.[3] Give temporary exemption. Submit VAERS report. Grant indefinite exemption, if warranted.	Immediate or prompt dermatology or other consult.[6] Give temporary exemption. Submit VAERS report. Grant indefinite exemption, if warranted.	Prompt neurology consultation.[5,6] Give temporary exemption. Submit VAERS report. Grant indefinite exemption, if warranted.	Seek consultation, as appropriate. Consider temporary exemption.[6] Submit VAERS report. Grant indefinite exemption, if warranted.

Clinical guidelines for managing adverse events after vaccination: *Version April 2003.* This document provides general guidance, to adapt to individual clinical cases. Use with companion tables. Patients may present with symptoms corresponding to more than one category. Revisions to this document will be disseminated via medical command channels and posted on AVIP site, www.anthrax.mil. The probability of events on this chart is not uniform: some are quite common and some are rare. See cover sheet for details.

Submit VAERS reports as warranted. Must be submitted for hospitalization, loss of duty ≥ 24 h, or suspected vial contamination. Other events may also be reported. Presumption of causation is not required to submit VAERS reports. Forms available at www.vaers.org.

Table 2A: Systemic Events (SE) After Vaccination: April 2003

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
<u>Systemic Events (SE):</u> Symptoms and signs of illness after vaccination. Any reaction that does not involve the injection site. Temporal relationship does NOT prove a cause-effect relationship, particularly if multiple vaccines were given and/or other specific diagnoses of illness have occurred.	**Health-care provider should provide appropriate diagnostic evaluation. In some cases, give pretreatment to avert symptoms with next vaccination, to avoid morbidity, but allowing for continued vaccination**.[2]	**If mild and self-limited, may proceed with next dose. Avoid multiple vaccines in one session for this patient, if possible. Credentialed health-care providers may make clinical decisions to alleviate future discomfort for individual Service Members who develop substantial or persistent reactions.**[7-8]	**VAERS reporting discussed in text.**
(SE 1a) Myalgias and/or Arthralgias: **(SE 1b) Arthritis:** • Primary • Secondary (exacerbation of existing condition)	Acetaminophen or NSAIDs may be administered. Pretreatment may be necessary.[2,4]	Subsequent doses can usually be given. Anthrax: For symptoms persisting > 96 h, seek specialty consultation. Consider temporary exemption until symptoms have resolved and evaluation is completed.	If persistent, start work-up to rule out other etiologies. Consult, if needed. VAERS report encouraged when symptoms persist > 96 hours. Notify VHC if symptoms persist > 2 weeks.[9]

Table 2B: Systemic Events (SE) After Vaccination: April 2003

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
(SE 2a) Mild "Viral"-Like Symptoms: At least three of the following, lasting < 96 hours: • Fever (100° to 102.5°F (adolescent/adult) or 104°F (children)) [oral equivalent] • Anorexia • Nausea • Myalgia • Arthralgia • Malaise • Fatigue • Light-headedness (colloquial "dizziness," but not true vertigo. See also **SE 19b**) • Headache (including photophobia or aching eyes) May be associated with moderate or large local reactions. Usually resolves spontaneously with no treatment or with analgesics and rest. ========== **(SE 2b) "Flu"-like or "Viral"-like**, not otherwise specified	-Options include analgesics or anti-emetics to treat complications or progression. Topical steroids and antihistamines for large local reactions.[1,2,4]	-Proceed with next dose, in most cases.[4] For fever > 102.5°F (adolescent / adult) or 104°F (children) [oral equivalent], consider benefit-risk ratio for continuing doses if patient or provider is concerned about risk with future doses.[5]	Consider treatment before or at time of next vaccination, particularly if large local reaction as well.[1,2,4] Consider **SE 17** if respiratory illness is the dominant feature. Consider **SE 18** if gastrointestinal illness is the dominant feature.
(SE 3) Severe and/or Prolonged Nonspecific Symptoms (sometimes called severe or prolonged "viral"-like illness): • Includes temperature > 102.5°F (adolescent/adult) or 104°F (children) [oral equivalent] • Includes temperature > 100.5°F and/or systemic symptoms lasting > 96 hours	-If consistent with serum sickness, may benefit from short course of oral prednisone, if not stabilized. May warrant consultation. -Evaluate for coincident disease and treat appropriately. High temperatures warrant consultation.	-Consult with next level of care. -Consider temporary exemption, pending consultation. -If unexplained by other causes may warrant contraindication.	VAERS report encouraged, if no other cause identified. Avoid simultaneous vaccination.

Table 2C: Systemic Events (SE) After Vaccination: April 2003

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
(SE 4) Headaches: **New Onset (SE 4a)** **Prior history, exacerbation of existing condition (SE 4b)** • Usually bi-temporal without migraine features, "tension type" or dominant feature of "viral-like" syndrome • Usually resolves in several days	-Acetaminophen 650-1000 mg orally every 4-6 h or ibuprofen 600-800 mg orally every 8 h (or other non-steroidal anti-inflammatory drugs, NSAIDs).[4]	-Proceed with next dose, unless worsening pattern. Start pre-treatment 1 h before next dose.[2] -Anthrax: For symptoms persisting > 96 h consider consultation.[9]	-Pretreatment generally effective.[2] -If pattern worsens, give temporary exemption, pending consultation with neurology. If referred, neurologist should submit follow-up VAERS report.
(SE 5) Nausea and/or Vomiting: • No other signs or symptoms of anaphylaxis • Usually resolves without treatment • Can be vasovagal	-Usually resolves without treatment, but standard anti-emetics and even (sedating) antihistamines may provide relief.[4]	-Proceed with next dose, with precautions for a vasovagal reaction. -Anthrax: For symptoms persisting > 96 h, consider consultation.	-Not reproducible from one injection to the next on initial observations, unless part of vasovagal reaction. Typically, no predictive value for more serious reaction.
(SE 6) Syncope or Near-Syncope (Fainting, Light-headedness) Shortly After Vaccination: • May be accompanied by prolonged malaise • Fainting or near-fainting with signs of vasovagal reaction (diaphoresis, nausea, vomiting, usually bradycardia, widening pulse pressure and/or frank hypotension) • May result in a fall with secondary injury • Asking before vaccination about this predisposition may avoid injury	-Position in sitting or supine position, with legs elevated head down, if needed. • Rarely requires atropine to reverse profound bradycardia. • Encourage hydration as soon as stabilized and before future injections. • Advise that future injections be given in supine position.	-Proceed, but with precautions as outlined under treatment. -Anthrax: If syncope or near-syncope was related to pain or burning at injection site after injection, consider route.[7]	-Occurs in about 1% of healthy, fit adults. -Procedures when giving injections of any kind should anticipate this reaction, to avoid traumatic injury.

Table 2D: Systemic Events (SE) After Vaccination: April 2003

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
(SE 7) Tinnitus: **New onset (SE 7a)** • Ringing in the ears developing within less than 1 to 2 weeks after an injection **Prior history (SE 7b)** • Worsening of pre-existing condition	-If nasal congestion present, consider treatment. -If symptoms persist > 1 to 2 weeks, consult with ear-nose-throat (ENT) specialist. -See VHC treatment algorithm for tinnitus.	-If symptoms do not resolve by next dose, consider temporary exemption, pending routine consultation with specialist.	-No well-defined association with any vaccine recognized at this time. -If event recurs with later dose, give temporary exemption, pending consultation.
(SE 8) Focal or Limited Skin Reaction, <u>not</u> near most recent injection site: • Take photo while acute. • Consider skin biopsy • Rule out urticarial lesion as cutaneous anaphylaxis	-Treat as clinically indicated, usually with antihistamines and topical corticosteroids. -Consult with dermatology, if symptoms persist.	-Subsequent doses can usually be given, but consider treatment to minimize symptoms.	-May be a rash, erythema, bruising, swelling, et cetera, at a distance from most recent injection site, such as at previous injection site. -May be unrelated to vaccination.
(SE 9) Generalized Skin Reaction (pruritic or non-pruritic), not suggestive of anaphylaxis: • Maculopapular or target lesions • Must involve skin sites remote from injection site, not just on the injection arm • Take photo while acute • Refer for skin biopsy if possible	-Give antihistamines (e.g., cetirizine or fexofenadine).[1] -Consider high-dose prednisone (50 to 60 mg daily for 5 to 7 days with rapid taper) if severe, but only after specific diagnosis. -If rash is early erythema multiforme, Stevens-Johnson, or toxic epidermal necrolysis, see section **SE 10**. Longer therapy may be needed. Note: accurate diagnosis may call for skin biopsy.	-Consider temporary exemption, pending routine consultation with specialist.	-In rare circumstances, additional vaccine doses may result in a more serious generalized skin reaction. -Additional doses should be given with caution after expert evaluation and consideration of benefit/risk ratio. -Strongly encourage submission of VAERS report, particularly if requiring treatment.

Table 2E: Systemic Events (SE) After Vaccination: April 2003

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
(SE 10) Diffuse Blistering Dermatitis and/or Mucositis: • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis • Others (fixed drug eruptions, etc.) • Skin biopsy indicated	-Treat acutely, record visually with photo; immediate dermatology and allergy consultation for full treatment program and follow-up. -Accurate diagnosis may call for skin biopsy.	Give temporary exemption, pending consultation.	-Submit VAERS report. There are no safety data for challenge dosing and/or desensitization of these types of potentially life-threatening skin reactions. -Probably warrants permanent exemption.
(SE 11) Anaphylaxis, Generalized Allergic Reaction: onset typically within the first few hours after vaccination but delayed presentation possible: • **Anaphylaxis:** Watery eyes, nasal congestion, general itching, hives, coughing, throat tightness, wheezing, short of breath, light-headed, rapid heart rate, hypotension, anxiety reaction ("sense of doom"), nausea, vomiting, diarrhea, loss of bladder or bowel control with loss of consciousness • **Generalized rash, itching and shortness of breath:** Treat as anaphylaxis, unless immediate evidence of other cause	-Potentially life-threatening allergic reaction, treat immediately with epinephrine. -Oral corticosteroid therapy prevents delayed-phase anaphylaxis, which can also become life threatening. -Admit to hospital if laryngeal edema or other life-threatening condition is present. Physician or other credentialed provider evaluation required.	Give temporary exemption, pending consultation with allergist.	-Submit VAERS report. Seek allergy consult.[3] -Review benefit-risk ratio carefully with patient. Consult patient regarding treatment options and further vaccination under controlled desensitization conditions. Avoid simultaneous vaccinations. -Permanent exemption may be required.
(SE 12) Angioedema/Swelling – Diffuse or distant from injection site, with or without pruritus within 2 weeks of vaccination: • If onset immediate (within ~ 2 h after injection) may be early cutaneous presentation of serious anaphylactic reaction (see **SE 11**) • If delayed onset (typically within 2 to 3 weeks), consider serum sickness	-If initial manifestation is consistent with anaphylaxis, treat as in **SE 11.** -If onset > 4 h, consider treating with corticosteroids and anti-histamines for 5 to 7 d. Note risk of relapse of serum sickness, if steroids are tapered too quickly. -Evaluate with CBC, ESR, CRP, LFTs, and UA. -Store serum sample before steroid therapy (may be sent to VHC).	Give temporary exemption, pending consultation with allergist and/or dermatologist.	-Submit VAERS report. Seek consult.[4] -Review benefit-risk ratio carefully with patient. Consult patient regarding treatment options and further vaccination under controlled desensitization conditions. -Permanent exemption may be required.

Table 2F: Systemic Events (SE) After Vaccination: April 2003

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
(SE 13) Neurologic Disease, Severe: Possible diagnoses include: • Peripheral neuropathy, nonfocal • Encephalopathy • Guillain-Barré syndrome • Progressive focal neurologic disease (see also **SE 14**) Assumes no other etiologic factor	Consult with neurology for diagnosis and treatment. -Some cases may benefit from rapid treatment with high-dose intravenous immunoglobulin. -Contact VHC Network for case management requirements.	Give temporary exemption, pending consultation with neurology.	-Submit VAERS report. -Consider risk for recurrent reaction before administering additional doses. -Permanent exemption may be required.
(SE 14) Focal Neurologic Disease: • Cranial nerve palsy, Bell's palsy • Neuropathy/neuritis • Radiculopathy • Paresthesias / blepharospasms • Optic neuritis • Ulnar nerve neuropathy (if diagnosis based on physical exam and/or nerve studies. If by symptoms only, give precedence to **LR7** group)	-Consider compression or trauma to ulnar nerve due to act of injection or hyperinflammatory response to vaccine adjuvants -Perform clinical work-up. -Consult with neurology.	Give temporary exemption, pending consultation with neurology. Emphasize injection in deltoid rather than triceps area.	Submit VAERS report. If persistent, specific treatment may be necessary after neurology consultation. Contact VHC Network for case management and follow-up VAERS tracking.
(SE 15) Prolonged Fatigue (> 60 days) [5] : < 50% functionality (work, recreation, school), compared to before vaccination • Loss of exercise tolerance • Non-restful sleep a frequent feature • Reduced concentration, decreased memory, as seen in many other chronic illnesses and/or depression	-Treat and consult appropriately before 60-day threshold. -Consult with specialty center with expertise in chronic fatigue and related syndromes. -Include sequential SF36v2 in evaluations. -Consider evaluation for sleep disorders.	Give temporary exemption, pending consultation.	-Currently no recognized association with any vaccine. -Cases are often eventually linked with other diagnoses. -Close follow-up and sequential evaluations may be warranted. -Submit VAERS report. Contact VHC Network for case management and follow-up VAERS.

Table 2G: Systemic Events (SE) After Vaccination: April 2003

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
(SE 16) Acute Anxiety Response:	-Educate. Reassure. -Treat according to clinical condition. May require additional risk communication counseling.	Anthrax: If response related to burning at injection site or related events, consider consultation.[7,8] Proceed with next dose in most cases.	Some personnel may benefit from psychiatry consultation to assist with diagnosis and management.
(SE 17) Respiratory Illness: Symptoms such as cough, coryza, congestion, sore throat and rhinorrhea with or without accompanying systemic symptoms **SE 2a** may also apply but this code identifies respiratory illness as the dominant feature	-Treat symptomatically. -If symptoms persist $\geq$ 2 weeks, consider other etiologies.	Proceed with next dose, in most cases.[4]	Contrast with **SE 2a**. Some patients may jointly experience **SE 17 and SE 2a**.
(SE 18) Gastrointestinal Illness: Symptoms such as vomiting and/or diarrhea, with accompanying systemic symptoms (e.g., loose stool, abdominal pain, gas, indigestion). Note that category **SE 5** includes uncomplicated nausea and/or vomiting. **SE 2a** may also apply but this code identifies gastrointestinal illness as the dominant feature.	-Treat symptomatically. If symptoms persist $\geq$ 2 weeks, consider other etiologies.	Proceed with next dose, in most cases.[4]	This category identifies individuals with more severe and prolonged gastrointestinal symptoms. Some patients may jointly experience **SE 18 and SE 2a**.
(SE 19a) Dizziness **(SE 19b) "True" Vertigo** • Dysequilibrium characterized by spinning or impulsion, often with nystagmus	-An agent such as meclizine or scopolamine may help symptoms of vertigo.	As clinically appropriate.	May be linked with prior ear disease or may be associated with certain drugs or dehydration.
(SE 20) Idiosyncratic Response(s) to Live Vaccine(s), for example: • Rash after measles, rubella, varicella, smallpox vaccines • Fever after yellow-fever vaccine • Abdominal cramps, diarrhea after oral typhoid vaccine	-Treat symptomatically -If symptoms persist > 2 w, consider other etiologies.	As clinically appropriate.	Live vaccine adverse events algorithms and tables pending.

Table 2H: Systemic Events (SE) After Vaccination: April 2003

(Note: The probability of events listed in these tables is not uniform. Some are quite common. Others occur rarely, if at all)

Adverse Event Definitions & Evaluation	Treatment & Management	Future Doses	Comments
(SE-xxx) Other Systemic Events: Contact VHC Network for assistance with VAERS report if problem is severe or prolonged and temporally associated with vaccine administration.	Treat according to clinical condition. Seek consults, as appropriate.	Base decision on complete medical evaluation and consideration of benefit-risk ratio.	Goal: Defining new adverse events temporally associated with vaccine administration. If problem is severe or prolonged, VHC Network consultation is indicated.

1 - Treatment program for moderate to large local reactions:

- Apply high-potency topical corticosteroid cream or ointment at least 2 to 3 times per day until reaction has resolved. Rarely requires oral corticosteroids (e.g., prednisone at 1 mg/kg or 50 to 60 mg per day for 3 to 4 days, tapering off by 10 to 20 mg per day over the next 2 to 4 days). Avoid unprotected sun exposure at the treated sites and use sunscreen aggressively.
- Avoid unprotected sun exposure at the treated site for at least 1 to 2 weeks and use sunscreen aggressively. For at least 3 to 4 days, avoid strenuous exercise using the arm that has received the vaccination.
- If itching/pruritus is present, use second-generation antihistamines such as fexofenadine (*Allegra*®) 180 mg daily (if a child or < 60 kg body weight, use 60 mg twice daily) or cetirizine (*Zyrtec*®) 5-10 mg daily. If not available, use first-generation antihistamines, recognizing sedating side effects.
- If swelling extends below elbow, a sling may be useful. Some vaccine recipients may benefit from an ice pack within first 24 hours. Consider cellulites or lymphangitis in evaluation.

2 - Pretreatment program to prevent future large local reactions:

- If localized itching was a dominant feature, pretreat with a second-generation antihistamine such as fexofenadine (*Allegra*®) 180 mg daily (if a child or < 60 kg body weight, use 60 mg twice daily) or cetirizine (*Zyrtec*®) 5-10 mg daily. Start at least 24 hours prior to vaccine administration. If not available, use first-generation antihistamines, recognizing sedating side effects. Continuing for 48 to 72 hours after the injection (longer if local reaction persists or reflares).
- .Avoid unprotected sun exposure at the treated sites, use sunscreen aggressively and avoid strenuous exercise as above.

Comment: Some vaccine recipients will tolerate these types of reactions less well than others, and may be apprehensive about the health risk from the next injection. Careful education and/or willingness to consult with specialists may prevent unnecessary polarization or potential refusal of subsequent vaccinations. Because most of these vaccine recipients can receive additional doses safely, it is important to avoid unnecessary indefinite exemptions, considering the threat and mortality risk of weaponized anthrax.

3 - Prototype Allergy-Immunology Evaluation: Anthrax vaccine skin testing (full-strength prick test, 1:1,000 then 1:100 volume/volume dilution intradermal) with both prick and intradermal histamine (histamine base: prick test 1 mg/ml, intradermal 0.1 mg/ml) and diluent controls (sodium chloride 0.9%). If patient understands risks and benefits of further vaccination and seeks desensitization, provide progressive dose challenge without pretreatment initially, treat any reactions appropriately, and pretreat subsequent doses as needed. Save serum from before and 3 to 4 weeks after procedure, to evaluate immune response later. Serum can be sent to central repository or local medical treatment facility (MTF) serum bank. Use generic consent form for serum collection for patient care, but specifying permission for subsequent use of sera for anonymous retrospective research.

4 - Treatment program for mild to moderate systemic events: Symptomatic treatment to prevent recurrence of adverse events has been very effective for many vaccines, including anthrax vaccine.

- Acetaminophen 650-1000 mg orally every 4-6 h or ibuprofen 600-800 mg every 8 h for pain/headache at time of shot or 1 h prior to shot.
- Additional treatment for nausea and other symptoms as indicated.

5 - Prolonged fatigue linked to vaccination is extremely rare, and has not been characterized as a well-defined vaccine-related adverse event. However, if the patient so desires, VAERS report may be filed. In many cases, other diagnoses are made when more extensive evaluation and follow-up occurs.

6 - Next level of care indicates review by provider with more specialized scope of practice.

7 - Route: DoD and USCG policy is to administer anthrax vaccine using the subcutaneous route, as described in the manufacturer's product labeling ("package insert"). However, a physician or other credentialled health-care provider may make a clinical decision, at the point of care, to attempt to alleviate future discomfort for an individual Service Member who developed a large or persistent injection-site reaction after an earlier dose of the anthrax vaccine. Administering the injection intramuscularly in the deltoid may alleviate severe reactions. Information to be provided to these Service Members as determined by the ACIP follows.

8 - Interval: Package insert states to administer the anthrax vaccine according to a 0-2-4 weeks; 6-12-18 months schedule with annual boosters. This does not preclude a credentialed healthcare provider from making clinical decisions for an individual Service Member who experienced a significant systemic event. According to the 2002 ACIP General Guidelines (see reference below) a dose may be delayed and a temporary exemption issued especially if symptoms have not resolved from a previous dose.

9 – VHC: The Walter Reed National Vaccine Healthcare Center may be contacted via the following methods:

Mailing address:	PO BOX 59606 Washington, DC 20012-0606
Telephone:	202-782-0411/DSN 662-0411
Fax:	202-782-4658
Email:	askVHC@na.amedd.army.mil
Web site:	www.vhcinfo.org

According to the guidelines of the Advisory Committee on Immunization Practices (**ACIP. Use of anthrax vaccine in the United States. *MMWR* 2000;49(RR-15)(Dec 15):1-20**, http://www.cdc.gov/mmwr/PDF/rr/rr4915.pdf or http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4915a1.htm):

> "At this time, ACIP cannot recommend changes in vaccine administration because of the preliminary nature of this information. However, the data in this report do support some flexibility in the route and timing of anthrax vaccination under special circumstances. As with other licensed vaccines, no data indicate that increasing the interval between doses adversely affects immunogenicity or safety. Therefore, interruption of the vaccination schedule does not require restarting the entire series of anthrax vaccine or the addition of extra doses."

Regarding immunogenicity considerations in individualizing medical treatment: "Because of the complexity of a six-dose primary vaccination schedule and frequency of local injection-site reactions (see Vaccine Safety), studies are under way to assess the immunogenicity of schedules with a reduced number of doses and with intramuscular (IM) administration rather than subcutaneous administration. Immunogenicity data were collected from military personnel who had a prolonged interval between the first and second doses of anthrax vaccine in the U.S. military anthrax vaccination program. Antibody to PA was measured by enzyme-linked immunosorbent assay (ELISA) at 7 weeks after the first dose. Geometric mean titers increased from 450 µg/mL among those who received the second vaccine dose 2 weeks after the first (the recommended schedule, n = 22), to 1,225 for those vaccinated at a 3-week interval (n = 19), and 1,860 for those vaccinated at a 4-week interval (n = 12). Differences in titer between the routine and prolonged intervals were statistically significant ($p < 0.01$)."

Regarding immunogenicity and safety considerations in individualizing medical treatment: "…a small randomized study was conducted among military personnel to compare the licensed regimen (subcutaneous injections at 0, 2, and 4 weeks, n = 28) and alternate regimens (subcutaneous [n = 23] or intramuscular [n=22] injections at 0 and 4 weeks).

Immunogenicity outcomes measured at 8 weeks after the first dose included geometric mean IgG concentrations and the proportion of subjects seroconverting (defined by an anti-PA IgG concentration of $\geq$ 25 µg/mL). In addition, the occurrence of local and systemic adverse events was determined. IgG concentrations were similar between the routine and alternate schedule groups (routine: 478 µg/mL; subcutaneous at 0 and 4 weeks: 625 µg/mL; intramuscular at 0 and 4 weeks: 482 µg/mL). All study participants seroconverted except for one of 21 in the intramuscular (injections at 0 and 4 weeks) group. Systemic adverse events were uncommon and similar for the intramuscular and subcutaneous groups. All local reactions (i.e., tenderness, erythema, warmth, induration, and subcutaneous nodules) were significantly more common following subcutaneous vaccination. Comparison of the three vaccination series indicated no significant differences between the proportion of subjects experiencing local reactions for the two subcutaneous regimens but significantly fewer subcutaneous nodules ($p < 0.001$) and significantly less erythema ($p = 0.001$) in the group vaccinated intramuscularly (P. Pittman, personal communication, USAMRIID, Ft. Detrick, MD)."

See also:

Advisory Committee on Immunization Practices. General recommendations on immunization. MMWR 2002;51(RR-2):1-35. (2002 Feb 8) ftp://ftp.cdc.gov/pub/Publications/mmwr/rr/rr5102.pdf

(info paper follows)

ANTHRAX VACCINE IMMUNIZATION PROGRAM
INFORMATION PAPER

SUBJECT: Route of Administration for Anthrax Vaccine 28 April 2003

1. PURPOSE. To describe an alternate route for administrating anthrax vaccine.

2. FACTS.

a. The US government license (approved by the Food and Drug Administration (FDA)) for anthrax vaccine is based on injecting the vaccine subcutaneously, about ½-inch under the skin. Subcutaneous (SC) injections place the vaccine in fatty tissue between the skin and underlying muscle. The anthrax vaccine was 92.5% effective in preventing anthrax infection when injected subcutaneously in a key study (Brachman, 1962; FDA, 1985).

b. In a small study, people given anthrax vaccine SC or IM were compared for antibody levels and side effects. The two groups developed roughly the same amount of antibodies. But people vaccinated by the SC route were more likely to develop tenderness, redness, warmth, swelling, or lumps at the injection site, compared to people vaccinated by the IM route. Other information shows that anthrax-fighting antibody levels are somewhat higher when the intervals between anthrax vaccinations are prolonged a few weeks longer than usual. These data come from the US Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, MD (ACIP, 2000).

c. Although it is DoD policy to follow the FDA-approved method of SC injections, this policy does not prevent a physician or other authorized health-care provider from making a clinical decision to use an IM injection in a special case. A special case could be to alleviate future discomfort for an individual Service Member who developed a large or persistent injection-site reaction or experienced a significant systemic event after an earlier dose of anthrax vaccine given by SC injection. In such a special case, IM administration is not prohibited if the health-care provider believes the injection will provide appropriate vaccine protection and reduce side effects, and informs the patient of the special circumstances.

d. The independent civilian panel known as the Advisory Committee on Immunization Practices reported that available data “do support some flexibility in the route and timing of anthrax vaccination under special circumstances. As with other licensed vaccines, no data indicate that increasing the interval between doses adversely affects immunogenicity or safety.”

3. REFERENCES.

a. Brachman PS, Gold H, Plotkin SA, Fekety FR, Werrin M, Ingraham NR. Field evaluation of a human anthrax vaccine. *American Journal of Public Health* 1962;52:432-45. http://www.anthrax.mil/media/pdf/field_eval.pdf.

b. Food & Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review. *Federal Register* 1985;50:51002-117. http://www.anthrax.mil/media/pdf/fed_reg.pdf.

c. Advisory Committee on Immunization Practices. Use of anthrax vaccine in the United States. *Morbidity & Mortality Weekly Report* 2000;49(RR-15):1-20. www.cdc.gov/mmwr/PDF/rr/rr4915.pdf.

COL John D. Grabenstein/DASG-HCA/703-681-5059

Approved by COL Randolph